Egyptian Journal of Ear, Nose, Throat and Allied Sciences (2014) **15**, 109–116

Egyptian Society of Ear, Nose, Throat and Allied Sciences

Egyptian Journal of Ear, Nose, Throat and Allied Sciences

www.ejentas.com

ORIGINAL ARTICLE

Diffusion-weighted MRI versus PET/CT in evaluation of clinically N0 neck in patients with HNSCC. Systematic review and meta-analysis study

Ossama Hassan *, Mohamed shehata Taha, Waleed Farag

Otolaryngology Department, Ain Shams University, Cairo, Egypt

Received 20 March 2014; accepted 8 April 2014
Available online 10 May 2014

KEYWORDS

cN0 neck;
Clinically negative neck;
HNSCC;
Head and neck squamous cell carcinoma;
PET/CT;
Diffusion weighted MRI

Abstract *Background:* Evaluation of a clinically N0 neck is essential in cases of head and neck squamous cell carcinoma (HNSCC) in order to determine whether the neck needs treatment or not.

Purpose: The study was designed to compare the efficacy of DW-MRI with that of PET/CT scans in the preoperative evaluation of clinically N0 neck in cases of HNSCC.

Methods: A systematic search was performed by the PubMed/MEDLINE to identify and select the relevant studies published within the last 20 years (up to 20/01/2014). Reported sensitivities, specificities, Positive Likelihood Ratio, Negative Likelihood Ratio and Diagnostic Odds Ratio were metaanalyzed. QUADAS criteria were used to evaluate the methodologic quality of the studies.

Results: Six studies met the inclusion criteria and were analyzed. Only one study evaluated DW-MRI whereas 5 studies evaluated PET/CT comprising a total sample size of 329 patients. Sensitivity was homogeneous across studies ($P = 0.202$), whereas specificity was heterogeneous across studies ($P = 0.050$). The overall sensitivity, specificity and accuracy rates of DW-MRI in evaluation of a clinically N0 neck were 100%, 71% and 85% respectively whereas PET/CT scans' overall sensitivity, specificity and accuracy were 68%, 84% and 78% respectively.

Conclusions: The available evidence suggests that DWI is more sensitive than PET/CT in the preoperative evaluation of cN0 neck in patients with HNSCC. PET/CT exam has low sensitivity and a positive test would not help the clinician in the management of the patient with clinically N0 disease and therefore, it should not be routinely used in neck nodal status work-ups.

* Corresponding author. Home address: 17 Hassan Aflaton Street, Ard Algolf, Madinet Nasr, Cairo, Egypt. Tel.: +20 (202) 24171137, mobile: +20 1000056207.
E-mail address: braveear58@yahoo.com (O. Hassan).

Peer review under responsibility of Egyptian Society of Ear, Nose, Throat and Allied Sciences.

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1. Introduction

Lymphatic metastasis is an important prognostic factor in patients with HNSCC. Regardless of the primary tumor site, the presence of a single metastatic lymph node in HNSCC reduces the 5-year survival rate by approximately 50%. The presence of bilateral metastatic lymph nodes in the neck

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http://dx.doi.org/10.1016/j.ejenta.2014.04.003

reduces the survival rate to about 25% of that of patients without nodal metastasis. Cervical lymph node metastases influence not only the risk of local recurrence but also the risk of distant metastases, making lymph node status one of the most important predictors of prognosis. Therefore, accurate assessment of the lymph node status is important for the choice of treatment.[1]

Cervical lymph node metastasis staged by palpation has been demonstrated to be inaccurate; the rate of occult cervical nodal metastases is at least 30% by simple palpation.[2] To avoid the unnecessary treatment of histologically negative necks, a staging technique must be sensitive enough to reduce the risk of occult metastases to less than 20%, which means a negative predictive value (NPV) of more than 80%.[3] With the development of modern imaging modalities, the American Joint Committee on Cancer has stated that clinical staging should include physical examination as well as the results of other imaging modalities. Research is now directed toward finding a staging method sensitive enough to bring the risk of occult metastases below 20%.

Previous meta-analyses compared the diagnostic accuracy of different imaging modalities in neck node evaluation. However, these studies looked at a mixture of cN+ and cN0 patients, and paucity of studies has focused only on patients with cN0 necks.

The aim of this study is to do a systematic review for the performance of DWI versus PET/CT in the evaluation of neck lymph node metastasis in clinically N0 neck of patients with HNSCC.

2. Methods

2.1. Search for relevant studies

Using MEDLINE database (www.pubmed.com), we conducted a systematic literature search to identify relevant studies published within the last 20 years (from 1995 up to 20/1/2014), which evaluated the role of PET/CT and DWI/MRI (in combination or separately) in diagnosis of cN0 neck in patients with HNSCC. Disease-specific search terms (cN0 neck, clinically negative neck, HNSCC, head and neck squamous cell carcinoma) were combined with diagnostic modality specific search terms (PET/CT, Positron emission tomography and computed tomography, DWI, Diffusion weighted MRI) in all our searches. The electronic searches were supplemented by scanning the reference lists from retrieved articles to identify additional studies that may have been missed during the initial search. It was decided to include only those studies which are published in the English language or translated to the English language; dealing with human subjects, including radiological procedures (PET/CT and or DWI/MRI) which are used in cN0 neck of patients with HNSCC. Also patients in the included studies did not receive any treatment before being evaluated by imaging techniques and histo-pathological study should be done to confirm the results of radiological imaging. In studies that included patients with different diseases, only those patients with HNSCC with cN0 were included. Excluded articles: are those articles which miss one or more of the above mentioned inclusion criteria, duplicated studies or those outdated by subsequent ones. Studies that provided insufficient data to construct a 2×2 contingency table were also excluded.

2.2. Study selection and data abstraction

From each relevant article, we abstracted the following information: type of the study (prospective, retrospective systematic review, meta-analysis or randomized control), number of cN0 neck of patients with HNSCC (population of the study), nature of the intervention (PET–CT scan and or DWI and histopathological examination of neck specimen), outcome and results (true +ve, false +ve, true −ve and false −ve cases).

To calculate sensitivity and specificity, true-positive (TP) was considered when PET/CT and/or DWI suggested the location of the metastatic cervical lymph node and was subsequently confirmed by histopathology, whereas false-positive (FP) was considered when this location was not confirmed. When PET/CT and/or DWI did not suggest the location of the metastatic cervical lymph node and was subsequently confirmed by histopathology, it was considered to be true-negative (TN). It was considered false-negative (FN) if the metastatic cervical lymph node was confirmed subsequently to negative PET/CT and DWI.

2.3. Quality assessment of primary studies

For each included study, the methodological quality was assessed by using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS) criteria, which is a 14-item instrument.[4] The questions in this checklist are aimed at establishing the validity of the study under review – that is, making sure that it has been carried out carefully, and that the conclusions represent an unbiased assessment of the accuracy and reliability of the test being evaluated. Each question covers an aspect of methodology that is thought to make a difference to the reliability of a study.

If the quality item is achieved, we give it (+), and (−) for the quality item not achieved or data not available. Fulfillment of the methodological quality criteria for the included articles was considered high, acceptable, or low, when the percentage of the mean (sum/total) of adherence for all included articles was >70%, 50–70%, or <50%, respectively.[5]

2.4. Statistical methods

The primary outcome for analysis is the diagnostic performance of DWI and PET/CT that detected the neck lymph node metastasis compared with the reference standard of neck dissection specimens. Sensitivity and specificity values were reported for individual studies. Pooled sensitivities and specificities of DWI and PET/CT in neck lymph node metastasis of cN0 neck from individual studies were calculated using a random effect model.[6] The random effect model incorporated the heterogeneity of the studies into the analysis of the overall efficacy. Likelihood ratios are metrics that are calculated using a combination of sensitivity and specificity values. The Positive Likelihood Ratio (LR+) is defined as the ratio of sensitivity (1− specificity), whereas the Negative Likelihood Ratio (LR−) is defined as the ratio of specificity (1− sensitivity). When a diagnostic test has absolutely no discriminating ability, both likelihood ratios equal 1. Metaanalysis of the collected data was conducted using the software: Meta-Disc© version 1.4.[7]

3. Results

3.1. Study identification and eligibility

Our search identified 1122 potentially relevant studies in MEDLINE (Table 1). Out of them, there were 406 potentially eligible studies. We excluded 217 out of the 406 studies because they miss one or more of the above mentioned inclusion criteria or were duplicated or were outdated by other more recent ones. Thus, 189 studies remained for possible inclusion and were retrieved in full text version. After reviewing the full article, 183 studies were excluded for the following reasons: some of them were essay studies while others were containing non cN0 neck or the primary was non HNSCC. Still other studies were containing neither DWI nor PET/CT or the pathological confirmation was not obtained in all cases or a 2×2 table could not be constructed. This process left 6 original articles which fulfilled all inclusion criteria and thus were included and used for further analyses.

3.2. Methodological quality assessment of the included studies

Systematic review of the included studies using QUADAS tool[4] revealed the following results (Table 2).

The total methodological quality score, expressed as a fraction of the maximum score, ranged from **9/14** (**64%**) to **13/14** (**93%**) with mean (**82%**) (High).

3.3. Analysis of included articles

Our searching of the Medline database revealed no studies comparing the role of DWI versus PET/CT in evaluation of cN0 neck in patients with HNSCC. So we divided our 6 included articles into two groups according to whether DWI or PET–CT scan was used alone for evaluation of cN0 neck in patients with HNSCC with the histopathologic analysis of the neck dissection specimen as the gold standard.

Group (A):
In this group, the patients underwent DWI. This group includes **13 cN0 neck sides** which represent the population of only one study. The detection rate (true positive) for DWI was 6 (46%) out of 13 neck sides, false-positive results were 2(15.5%) out of 13 neck sides, false- negative results were zero (zero%) out of 13 neck sides and the true negative results were 5(38.5%) out of 13 neck sides (Table 3).

Table 1 Detailed literature search.

Keywords	Number of articles and their abstracts	Potentially eligible studies
DWI versus PET/CT in HNSCC	0	0
DWI versus PET/CT	5	1
Diffusion weighted MRI versus positron emission tomography and computed tomography	14	2
DWI in clinically negative neck	0	0
DWI in cN0 neck	0	0
DWI in HNSCC	10	7
DWI in head and neck squamous cell carcinoma	18	7
Diffusion weighted mri in cN0 neck	1	1
Diffusion weighted mri in clinically negative neck	1	1
Diffusion weighted mri in head and neck squamous cell carcinoma	67	26
Diffusion weighted mri in head and neck squamous cell carcinoma (as a title)	5	5
Diffusion weighted mri in HNSCC	30	11
Diffusion weighted imaging in head and neck squamous cell carcinoma	54	26
Diffusion weighted imaging in clinically negative neck	1	1
Diffusion weighted imaging in cN0 neck	1	1
Diffusion weighted imaging in HNSCC	26	12
PET/CT in clinically negative neck	16	12
PET/CT in cN0 neck	3	3
PET/CT in HNSCC	60	33
PET/CT in head and neck squamous cell carcinoma	195	98
Positron emission tomograghy and computed tomography in cN0 neck	6	4
Positron emission tomograghy and computed tomography in clinically negative neck	44	7
Positron emission tomography and computed tomography in HNSCC	97	36
Positron emission tomography and computed tomography in head and neck squamous cell carcinoma	460	108
Positron emission tomography and computed tomography in head and neck squamous cell carcinoma. (as a title)	8	4
Total	1122	406

Table 2 QUADAS tool for methodological quality assessment of included studies.

No.	Study	Quality items														Quality score	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	Ratio	Percentage (%)
1	Dirix et al.[8]	+	+	+	–	+	+	+	+	+	–	–	+	+	+	11/14	79
2	Cetin et al.[9]	+	+	+	+	+	+	+	+	+	–	–	+	+	+	12/14	86
3	Chauhan et al.[10]	+	+	+	+	+	+	+	+	+	+	–	–	+	+	12/14	86
4	Nahmias et al.[11]	+	+	+	+	+	+	+	+	+	+	–	+	+	+	13/14	93
5	Ozer et al.[12]	+	+	+	–	–	+	+	–	+	–	–	+	+	+	9/14	64
6	Schoder et al.[13]	+	+	+	–	+	+	+	+	+	+	–	+	+	+	12/14	86

NB: (+) = the quality item achieved while (–) = the quality item not achieved or data not available.

Table 3 Reported detection rate for DWI in Group A.

No.	Study	Neck sides	DWI			
			TP	FP	FN	TN
1	Dirix et al.[8]	13	6	2	0	5

No. = numbers of the study, TP = true positive, FP = false positive FN = false negative, TN = true negative.

Table 4 Reported detection rate for PET/CT in Group B.

No.	Study	Neck sides	PET/CT			
			TP	FP	FN	TN
2	Cetin et al.[9]	36	16	6	3	11
3	Chauhan et al.[10]	51	15	1	6	29
4	Nahmias et al.[11]	49	13	4	4	28
5	Ozer et al.[12]	144	26	18	20	80
6	Schoder et al.[13]	36	6	4	3	23
	Total	316	76	33	36	171

No. = number of the study, TP = true positive, FP = false positive FN = false negative, TN = true negative.

Group (B):

In this group, the patients underwent PET/CT. This group includes **316 cN0 neck sides** which represents the population of 5 studies. The detection rate (true positive) for PET/CT was 76 (24%) out of 316 neck sides, false-positive results were 33(10%) out of 316 neck sides, false-negative results were 36 (11%) out of 316 neck sides and the true negative results were 171(54%) out of 316 neck sides (Table 4).

The pooled sensitivity of PET/CT is 68%. There is no significant heterogeneity in studies of Group B as the p value of chi-square test was 0.202 (>0.1) and I^2 index was 32.9% (<50%) (Fig. 1).

The pooled specificity of PET/CT is 84%. There is significant heterogeneity between the specificity of PET/CT in evaluation of cN0 neck in studies of Group B as the p value of chi-square test was 0.050 (<0.1) and I^2 index was 57.9% (>50%) (Fig. 2).

The pooled Positive Likelihood Ratio of PET/CT is 3.89. There is no significant heterogeneity in studies of Group B as The p value of cochran-Q test was 0.131 (>0.1), I^2 index was 43.6% (<50%) and Tau-squared index was 0.136 (<1) (Fig. 3).

The pooled Negative Likelihood Ratio of PET/CT is 0.39. There is no significant heterogeneity in studies of Group B as the p value of cochran-Q test was 0.281 (>0.1), I^2 index was 20.9% (<50%) and Tau-squared index was 0.034 (<1) (Fig. 4).

The pooled Diagnostic Odds Ratio of PET/CT is 11.96. There is no significant heterogeneity in studies of Group B as the p value of cochran-Q test was 0.185 (>0.1), I^2 index was 35.4% (<50%) and Tau-squared index was 0.294 (<1) (Fig. 5).

The prevalence rates of occult metastases in cN0 neck in patients of groups A, B and total patients were 46%, 35% and 36% respectively (Table 5).

3.4. Diagnostic accuracy

The sensitivity of DWI for the diagnosis of cN0 neck in patients with HNSCC was 100%, specificity (71%), positive predictive value (75%), negative predictive value (100%) and accuracy (85%). On the other hand, the sensitivity of PET/CT for the diagnosis of cN0 neck in patients with HNSCC was 68%, specificity (84%), positive predictive value (70%), negative predictive value (83%) and accuracy (78%) (Table 6).

4. Discussion

The optimal method for managing cN0 neck in SCC of the head and neck remains controversial. In 1994, Weiss et al.[3] recommended with decision analysis that when the probability of occult cervical metastases is more than 20%, the neck should be electively treated. Many staging techniques have been described for the preoperative staging of the cN0 neck in HNSCC in order to lower the amount of false-negative necks to 20% or less. This could lead to a change in treatment for this group of patients by avoiding SND in patients with a cN0 neck, thereby reducing postoperative morbidity.

Recently, DWI and PET/CT are new non-invasive diagnostic tools used for the evaluation of cN0 neck in patients with HNSCC.[14,15]

There were no studies comparing the role of DWI versus PET/CT in evaluation of cN0 neck in patients with HNSCC, so we divided the included studies into 2 groups; then we compared the results of both groups. Havenith et al. adopted this method.[16]

The present study revealed generally high quality scores of the included studies (Table 2); suggesting that most of included studies presented enough information overall and satisfied most of the requirements established. However most of studies

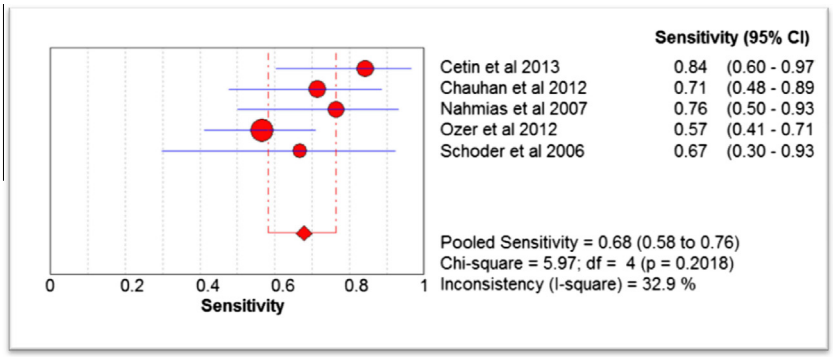

Figure 1 Forest plot showing the sensitivity of PET/CT in evaluation of cN0 neck in studies of Group B.

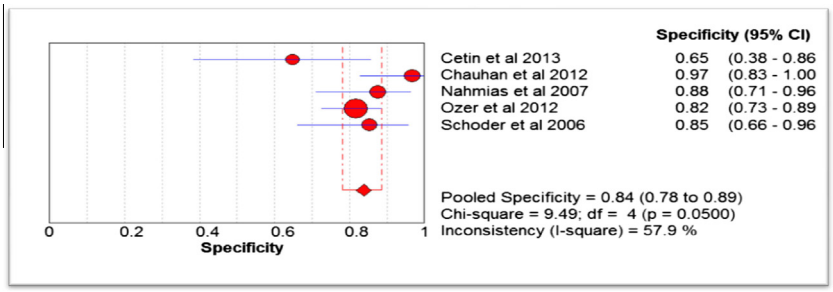

Figure 2 Forest plot showing the specificity of PET/CT in evaluation of cN0 neck in studies of Group.

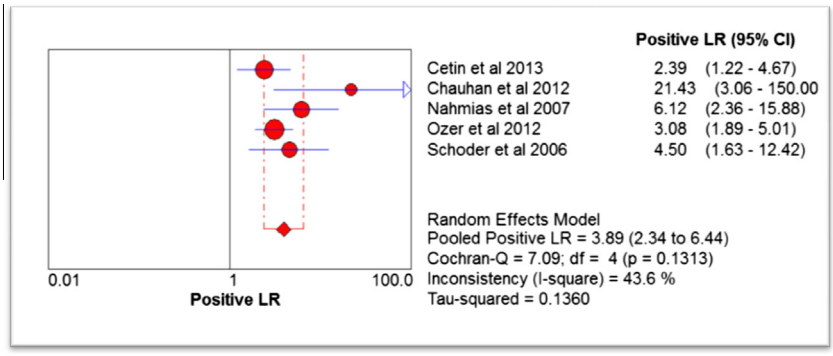

Figure 3 Forest plot showing the Positive Likelihood Ratio (random effects model) of PET/CT in evaluation of cN0 neck in studies of Group B.

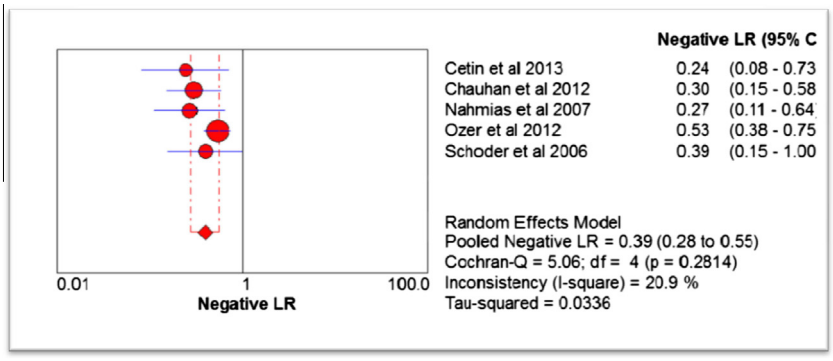

Figure 4 Forest plot showing the Negative Likelihood Ratio (random effects model) of PET/CT in evaluation of cN0 neck in studies of Group B.

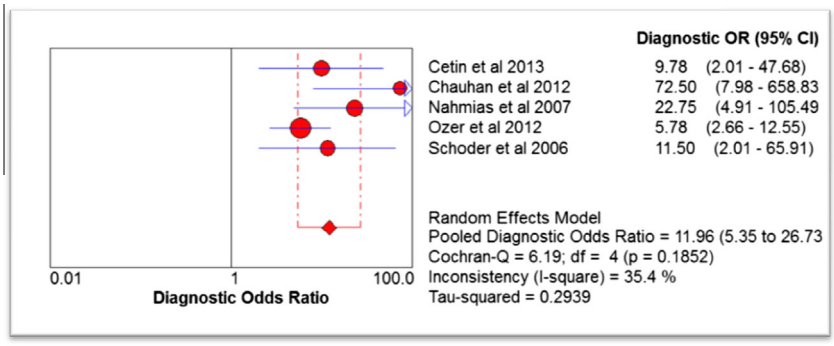

Figure 5 Forest plot showing the Diagnostic Odds Ratio (random effects model) of PET/CT in evaluation of cN0 neck in studies of Group B.

Table 5 The prevalence rates of occult metastases in cN0 neck in patients with HNSCC of Group A, B and total patients.

Patients	Positives by histopathological examination (true +ve and false −ve)	Prevalence rate (%)
Group A	6 out of 13 patients	46
Group B	112 out of 316 patients	35
Total patients	118 out of 329 patients	36

had a suboptimal design in regard to the blinding method (Item 11) as the interpretation of the histopathological examination results was done with the knowledge of the imaging results. Also the time period between histopathological examination and imaging techniques (DWI and PET/CT) (Item 4) was not mentioned in 3 articles, so our recommendation to all the researchers is to pay attention to these points to avoid bias.

The results of DWI in the present study revealed a high sensitivity (100%) and intermediate specificity (71%) whereas Bondt et al.[17] reported 92.3% sensitivity and 83.9% specificity. This minor discrepancy might be due the inclusion of 3 cN1 among the 17 neck sides in Bondt et al.[17] study.

There is no significant heterogeneity between the sensitivity, Positive Likelihood Ratio, Negative Likelihood Ratio and Diagnostic Odds Ratio in the included studies of Group B (Figs. 1 and 3–5), while there was significant heterogeneity between the specificity (Fig. 2) and this was the reason to adapt a random effect model for data pooling.[18]

A likelihood ratio greater than 1 indicates that the test result is associated with the presence of the disease, whereas a likelihood ratio less than 1 indicates that the test result is associated with the absence of disease. The further likelihood ratios are from 1 the stronger the evidence for the presence or absence of disease. Likelihood ratios above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively in most circumstances.[19] In the present study, the pooled Positive Likelihood Ratio of PET/CT is 3.89 (Fig. 3). This means that a person with cN0 neck having metastatic lymphadenopathy is about 4 times more likely to have a positive test than a person with cN0 neck who has not got metastatic lymphadenopathy in cases of HNSCC. On the other hand, the pooled Negative Likelihood Ratio of PET/CT is 0.39 (Fig. 4), indicating that the probability of having a negative test for individuals with metastatic lymphadenopathy in cN0 neck is 0.39 times of that of those without metastatic lymphadenopathy in cN0 neck of patients with HNSCC.

The Diagnostic Odds Ratio (DOR) of a test is the ratio of the odds of positivity in diseased relative to the odds of positivity in nondiseased. Alternatively, the DOR can be read as the ratio of the odds of disease in test positives relative to the odds of disease in test negatives. The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A value of 1 means that a test does not discriminate between patients with the disorder and those without it. Values lower than 1 point to improper test interpretation (more negative tests among the diseased).[20] In the present study, the pooled Diagnostic Odds Ratio of PET/CT is 11.96 (>1) (Fig. 5). This means that for the PET/CT the odds for positivity among cN0 neck of subjects with metastatic lymphadenopathy is nearly 12 times higher than the odds for positivity among cN0 neck of subjects without metastatic lymphadenopathy.

The pooled sensitivity (68%) and specificity (84%) of PET/CT in the present study were slightly discordant with that of Krabbe et al.[21] (64% and 81% respectively). This might be due to the lower intravenous dose of 18F-FDG (4 MBq/kg body weight with a maximum of 333 MBq) used in Krabbe et al.[21] than that used in the present study (not lower than 370 MBq of 18F-FDG).

In our study, DW-MRI presents high sensitivity (100%), Positive predictive value (75%), Negative predictive value (100%), accuracy (85%) and less specificity (71%) than PET/CT (68% sensitivity, 70% Positive predictive value, 83% Negative predictive value, 78% accuracy and 84% specificity) in the preoperative evaluation of clinically N0 neck in cases of HNSCC (Table 6). These results of DWI indicate the existence

Table 6 Diagnostic performance of DWI and PET/CT in evaluation of cN0 neck in both groups.

Diagnostic tool	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
DWI	100	71	75	100	85
PET/CT	68	84	70	83	78

of few false-negative and positive results, an important feature in the management of oncologic patients that could suggest the utility of DW-MRI in the initial stages of evaluation of cN0 neck of subjects with HNSCC. Also the results of PET/CT translates to 17% of necks with negative imaging results actually being metastatic, nearly 1 neck in 5 would have undetected disease; if untreated, the residual nodal tumor would presumably progress to the detriment of the patient. On the other hand, 30% of necks identified as positive would contain no disease; these patients may have unnecessary treatment. This leads to the conclusion that a positive test would not help the clinician in the management of the patient with clinically N0 disease.

The higher sensitivity of DWI is probably due to the fact that the majority of the LNs were subcentimetric. This is because the DW-MRI can detect behavior changes in tissues before they are visible to the naked eye.[22] Several factors enable the detection of small nodal metastases at DW-MRI; Use of improved echo-planar imaging technology, dedicated coils, and dedicated sequence optimization enables a maximal reduction of echo-planar imaging-related artifacts at a relatively high spatial resolution,[23] on the other hand, PET has limitations in detecting micro metastasis, related to spatial resolution of current PET cameras and partial volume effects.[24] The false negative results in PET/CT may arise due to tumor necrosis, fluorodeoxyglucose is not a cancer-specific agent, neutrophils and macrophages during an ongoing inflammatory or granulomatous processes show increased FDG accumulation and cause false-positive PET scans for malignancy.[12]

The prevalence rate of occult metastasis in cN0 neck in patients with HNSCC was **46%** in Group A, **35%** in Group B **and 36%** in general (Table 5). This percentage is similar to those reported by other studies which have reported prevalence rates ranging from **24%** to **50%**.[25,26]

The limitations of our study are the presence of only one study in group 1 and therefore no metaanalysis was done in this group, also most of the tumors included were T1 and T2, which could bias the results for the whole cN0 group of patients.

5. Conclusions

The available evidence suggests that DWI is more sensitive than PET/CT in the preoperative evaluation of cN0 neck in patients with HNSCC. This indicates the existence of few false-negative results, an important feature in the management of oncologic patients that could suggest its utility in the initial stages of the management process. PET/CT exam has low sensitivity and a positive test would not help the clinician in the management of the patient with clinically N0 disease and therefore, it should not be routinely used in neck nodal status work-ups.

6. Recommendations

- Multi-center prospective randomized double blind controlled trials comprising larger patient cohorts comparing between the roles of DW-MRI versus PET/CT in evaluation of cN0 neck in patients with HNSCC are required.
- Values of ADC and SUV of fluorodeoxyglucose must be defined in these trials.
- Researchers should pay attention to fulfill QUADAS items specially the blinding method and the time period between the imaging techniques and histopathological examination.

References

1. Mack MG, Rieger J, Baghi M, Bisdas S, Vogl TJ. Cervical lymph nodes. *Eur J Radiol*. 2008;66:493–500.
2. van den Brekel MW, Castelijns JA, Stel HV, Golding RP, Meyer GB, Snow GB. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. *Eur Arch Otorhinolaryngol*. 1993;250:11–17.
3. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg*. 1994;120:699–702.
4. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol*. 2003;10(3):25.
5. Delgado-Bolton RC, Fernández-Pérez C, González-Maté A, Carreras JL. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. *J Nucl Med*. 2003;44(8):1301–1314.
6. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58:982–990.
7. Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol*. 2006;6:31.
8. Dirix P, Vandecaveye V, De Keyzer F, et al. Diffusion-weighted MRI for nodal staging of head and neck squamous cell carcinoma: impact on radiotherapy planning. *Int J Radiat Oncol Biol Phys*. 2010;76(3):761–766.
9. Cetin B, Atasever T, Akdemir UO, et al. The role of positron emission tomography with 18F-fluorodeoxyglucose in nodal staging of clinical and radiolological N0 head and neck cancer. *Eur Arch Otorhinolaryngol*. 2013;270(8):2307–2313.
10. Chauhan A, Kulshrestha P, Kapoor S, et al. Comparison of PET/CT with conventional imaging modalities (USG, CECT) in evaluation of N0 neck in head and neck squamous cell carcinoma. *Med J Armed Forces India*. 2012;68(4):322–327.
11. Nahmias C, Carlson ER, Duncan LD, et al. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. *J Oral Maxillofac Surg*. 2007 Dec;65(12):2524–2535.
12. Ozer E, Naiboğlu B, Meacham R, Ryoo C, Agrawal A, Schuller DE. The value of PET/CT to assess clinically negative necks. *Eur Arch Otorhinolaryngol*. 2012;269(11):2411–2414.
13. Schöder H, Carlson DL, Kraus DH, et al. 18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI. *J Nucl Med*. 2006;47(5):755–762.
14. Herneth AM, Mayerhoefer M, Schernthaner R, Ba-Ssalamah A, Czerny Ch, Fruehwald-Pallamar J. Diffusion weighted imaging: lymph nodes. *Eur J Radiol*. 2010;76(3):398–406.
15. Agarwal V, Branstetter 4th BF, Johnson JT. Indications for PET/CT in the head and neck. *Otolaryngol Clin North Am*. 2008;41(1):23–49.
16. Havenith S, Lammers M, Tange R, et al. Hearing preservation surgery: cochleostomy or round window approach? A systematic review. *Otol Neurotol*. 2013;34:667–674.

17. de Bondt RB, Hoeberigs MC, Nelemans PJ, et al. Diagnostic accuracy and additional value of diffusion-weighted imaging for discrimination of malignant cervical lymph nodes in head and neck squamous cell carcinoma. *Neuroradiology*. 2009; 51(3):183–192.
18. Egger M, Smith GD, Altman DG. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd ed. London: BMJ Publishing Group; 2001.
19. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. 2004;329(7458):168–169.
20. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol*. 2003;56(11):1129–1135.
21. Krabbe CA, Balink H, Roodenburg JL, Dol J, de Visscher JG. Performance of 18F-FDG PET/contrast-enhanced CT in the staging of squamous cell carcinoma of the oral cavity and oropharynx. *Int J Oral Maxillofac Surg*. 2011;40(11):1263–1270.
22. Galbán S, Lemasson B, Williams TM, Li F, Heist KA, Johnson TD. DW-MRI as a biomarker to compare therapeutic outcomes in radiotherapy regimens incorporating temozolomide or gemcitabine in glioblastoma. *PLoS One*. 2012;7:e35857.
23. Vandecaveye V, De Keyzer F, Nuyts S, et al. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. *Int J Radiat Oncol Biol Phys*. 2007;67(4):960–971.
24. Crippa F, Leutner M, Belli F, et al. Which kinds of lymph node metastases can FDG PET detect? A clinical study in melanoma. *J Nucl Med*. 2000;41:1491–1494.
25. Spiro RH, Morgan GJ, Strong EW, Shah JP. Supraomohyoid neck dissection. *Am J Surg*. 1996;172:650–653.
26. van den Brekel MW, Castelijns JA, Snow GB. Imaging of cervical lymphadenopathy. *Neuroimaging Clin N Am*. 1996;6(2):417–434.